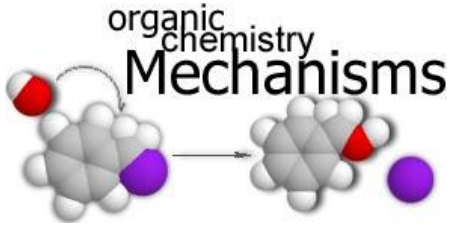
CHEM 344

ORGANIC REACTION MECHANISM



FOR CHEMISTRY' STUDENTS, COLLEGE OF SCIENCE

PRE-REQUISITES COURSE; CHEM 241

CREDIT HOURS; 2 (2+0+0)

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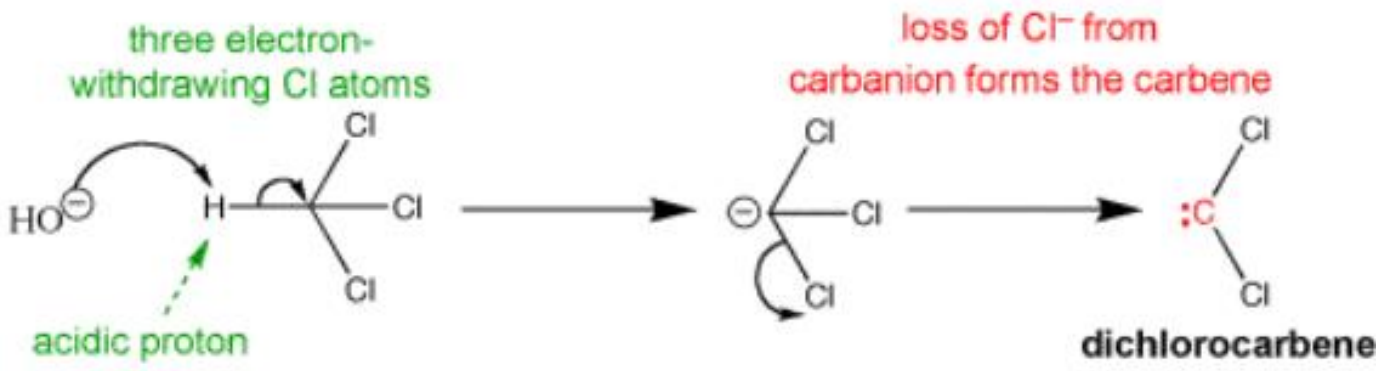
Elimination Reactions

TYPES OF ELIMINATION REACTIONS

- Elimination reactions, *are those reactions in which hydrogen along with a leaving group will be eliminated.*
- Elimination reactions *are used for the generation of double and triple bonds from a saturated compounds*.
- Based on the position of eliminating groups, *elimination reactions are classified as*:
  - α-Elimination

    Both groups are lost from the same atom to give a carbene.

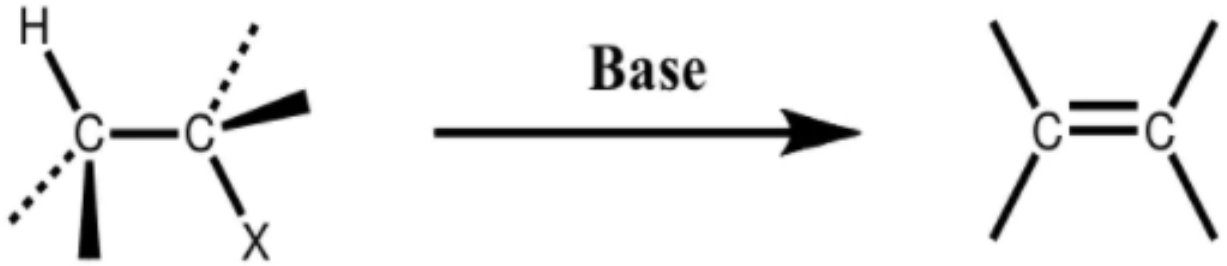


Unstable species are formed, which undergo further reactions.

TYPES OF ELIMINATION REACTIONS

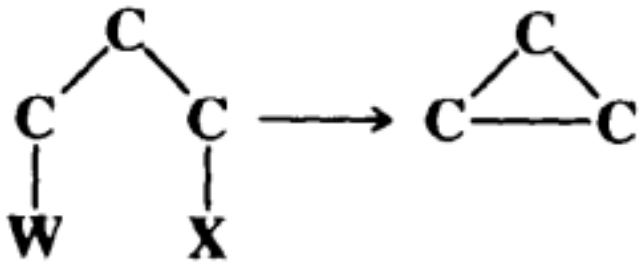
- **β -Elimination**

  Both groups are lost from the two adjacent carbon atoms to give alkene.



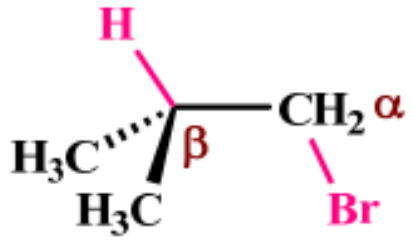
- **γ -Elimination**

  A three-membered ring is formed



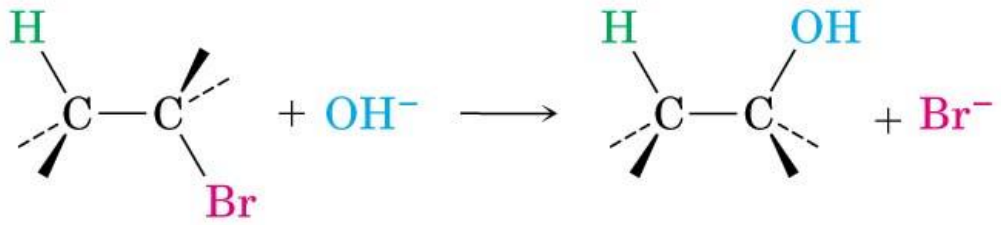
B-ELIMINATIONS

- **β–elimination** proceeds through two mechanisms;
  - E2 biomolecular elimination reactions
  - E1 unimolecular elimination reactions

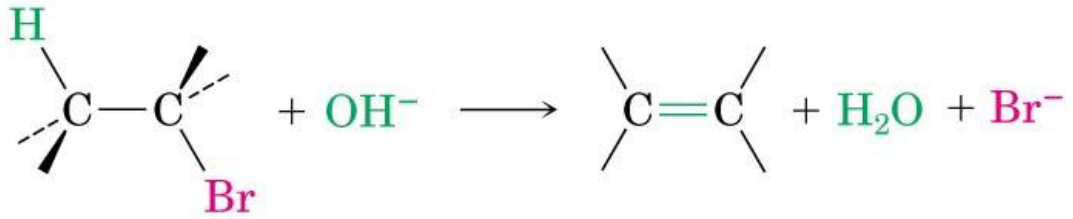


- E2 & E1 mechanism differ in the *timing of bond cleavage and bond formation*, analogous to the S_N2 & S_N1 mechanisms
- E2 & S_N2 reactions have some features in common, as do **E1 & S_N1 reactions.**

Substitution

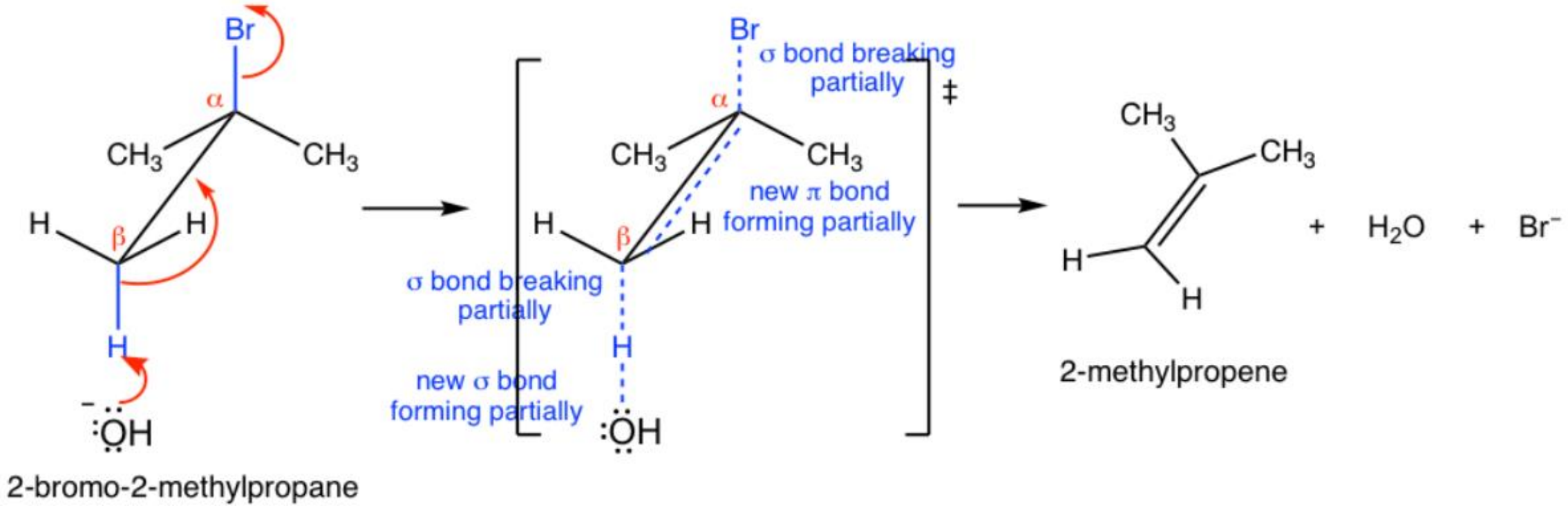


Elimination



REACTION MECHANISM

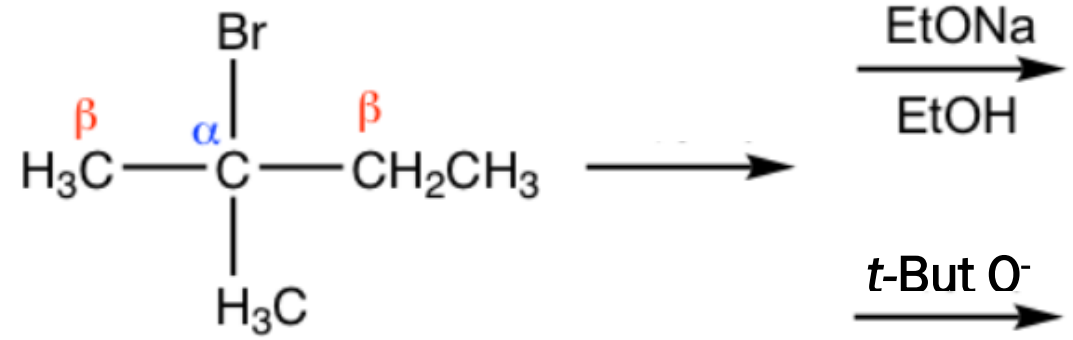
- E2 reaction is a single step elimination, with a single transition state



REGIOSELECTIVITY OF E2 REACTION:

For alkyl halides, if there are different β-carbons in the substrate, then the elimination reaction may yield more than one products.

- **Example:** **Dehydrohalogenation of 2-bromo-2-methylbutane** can produce two products, ***2-methyl-2-butene*** and ***2-methyl-1-butene***

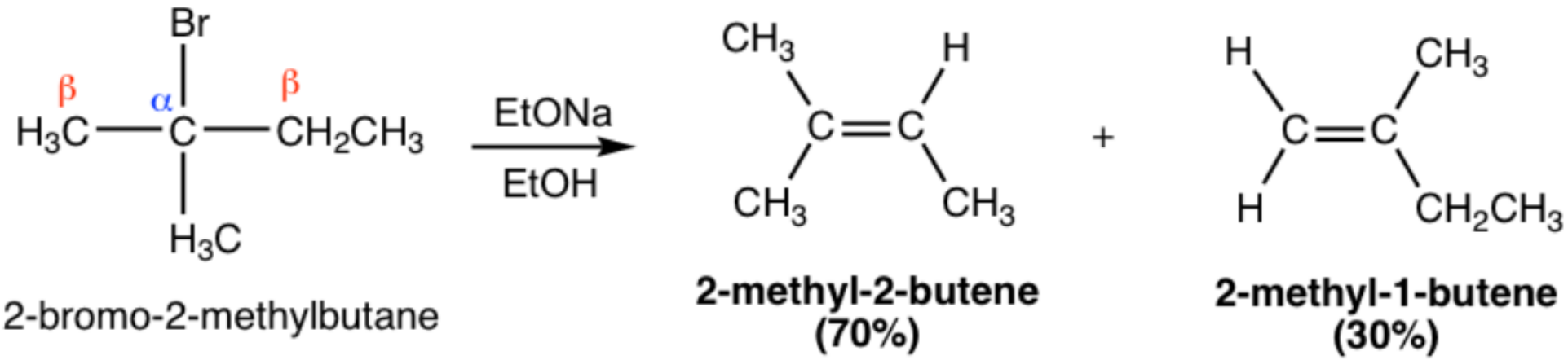


2-bromo-2-methylbutane

REGIOSELECTIVITY OF E2 REACTION:

Zaitsev's Rule

When small base, such as OH^-, CH_3O^-, EtO^-, is applied, the elimination products can be predicted by Zaitsev's rule, i.e. the major product is the more stable product - the one with the more substituted double bond.



2-bromo-2-methylbutane

2-methyl-2-butene (70%)

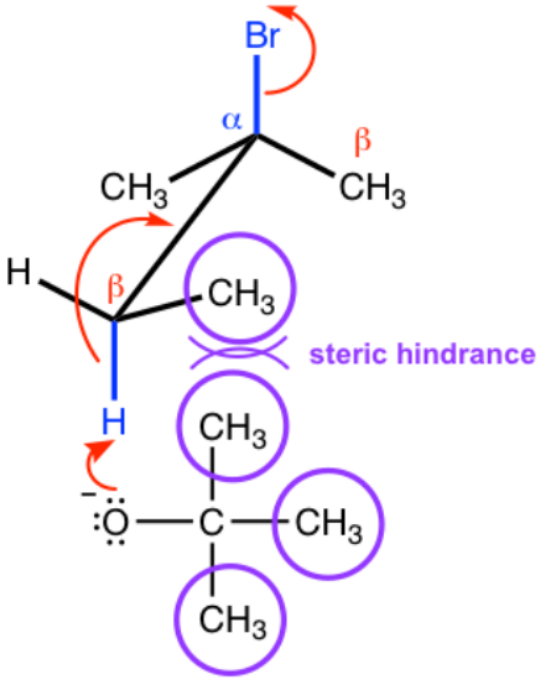
2-methyl-1-butene (30%)

REGIOSELECTIVITY OF E2 REACTION:

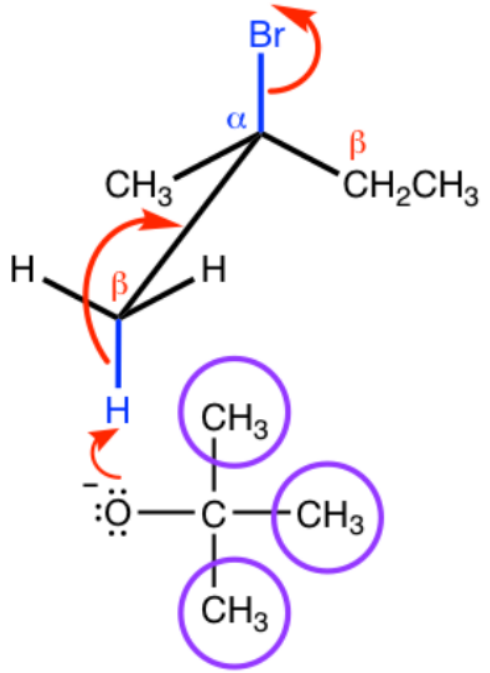
Hofmann's Rule

If a bulky base such as t-BuOK, is applied in the elimination, the reaction favors the formation of less substituted double bond.

This is mainly because of *Steric Hindrance*.



pathway (a): bulky base t-BuO⁻ is more hindered



pathway (b): bulky base t-BuO⁻ is less hindered

REACTION KINETICS

- The **E2 reaction** is a *concerted process* (one step reaction), with a *bimolecular rate-determining step*.

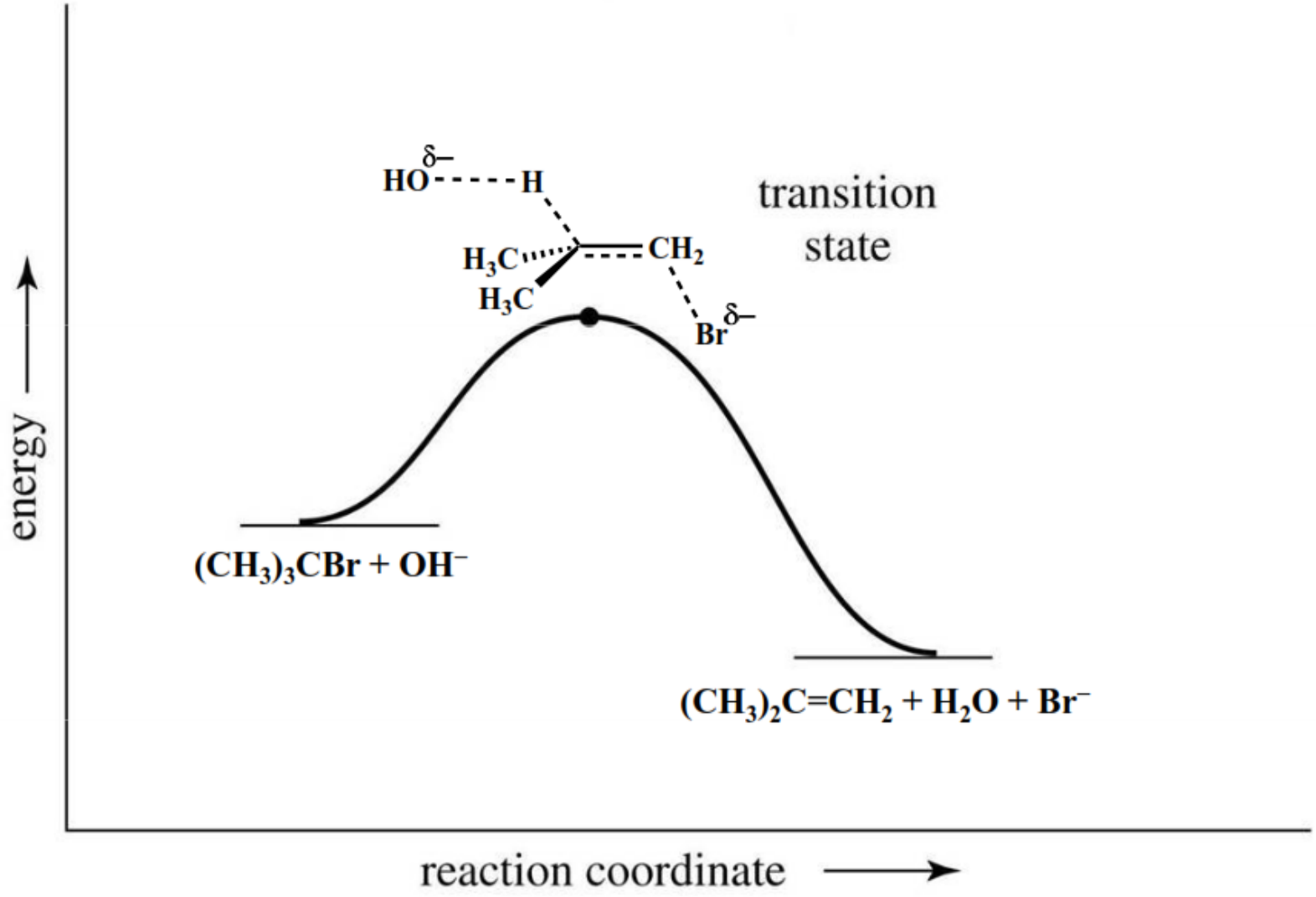
  "***Concerted***" means that the formation of a double bond, and departure of the leaving group (X^- and H^+) all occur in one step.

- The reaction rate is *second order*, because it's influenced by both the *alkyl halide* and *the base* (bimolecular).

$$\textbf{Rate} = k\,[R\text{-}X][B:]$$

- Reaction goes faster with stronger base and better leaving group.

ENERGY PROFILE DIAGRAM



FACTORS AFFECTING THE RATE OF E2 REACTION

- **E2 & S_N2 reactions** have some features in common in how the identity of the *base*, the *leaving group* and the *solvent affect the rate*.
- The rate of the E2 reaction increases with
  - the *strong, negatively charged bases* like ^-OH and ^-OR.
  - the *Polar aprotic solvents*
  - the *better the leaving group*.
- Rate of reaction follows the order,

most reactive — RI > RBr > RCl > RF — least reactive

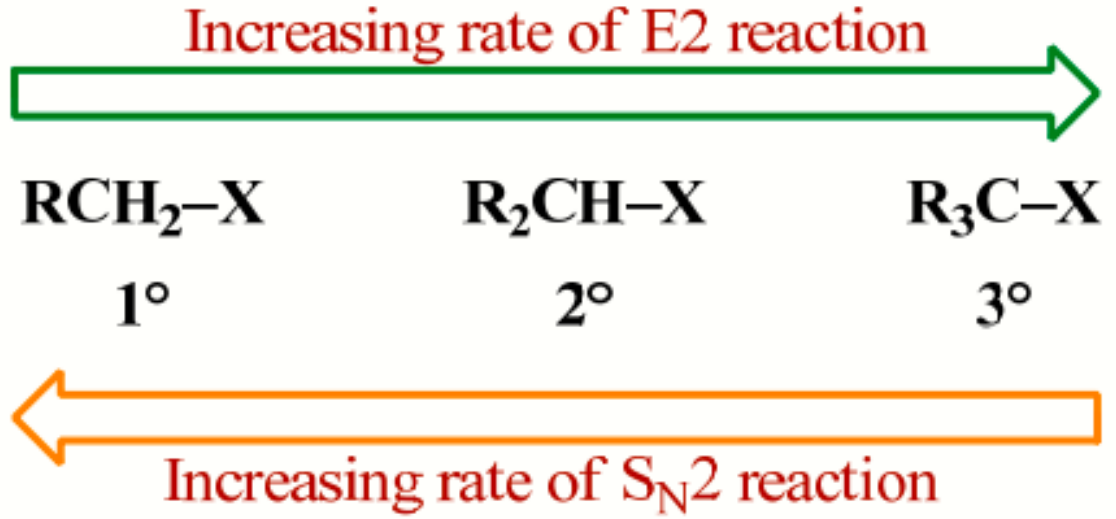
  - Alkyl iodides are the most reactive
  - alkyl fluorides the least reactive

} *because weaker bases are better leaving groups*

FACTORS AFFECTING THE RATE OF E2 REACTION

- The S_N2 and E2 mechanisms differ in how the R group affects the reaction rate.

  As the number of R groups on the carbon with the leaving group increases, the rate of the E2 reaction increases.

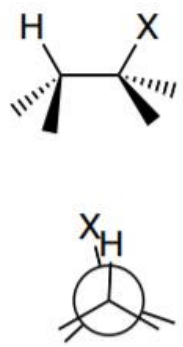


- In the transition state;
  - *The double bond is partially formed.*

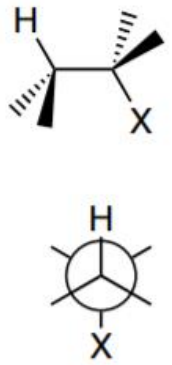
    Thus, the transition state for a more substituted alkene is lower in energy, reducing the activation energy for the reaction and making the reaction faster.

STEREOCHEMISTRY

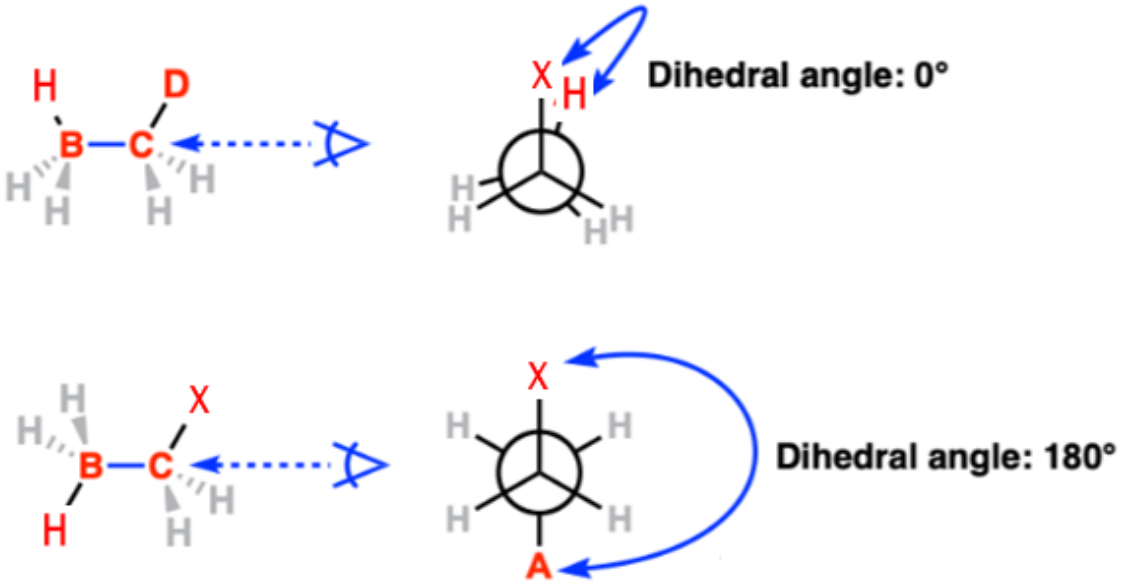
- The H being abstracted and the leaving group must be in the same plane



Syn periplanar:
the H and X
are eclipsed
dihedral angle = 0 °



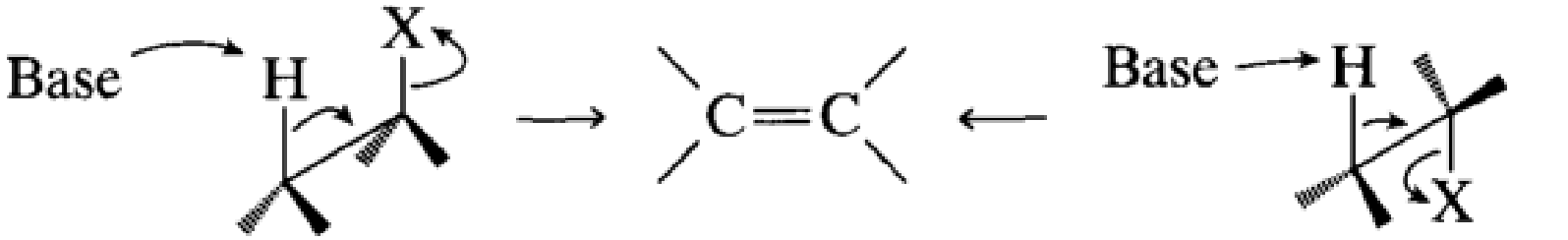
Anti periplanar:
the H and X are
anti staggered
dihedral angle = 180 °



- **Staggered conformation** has a lower potential energy
- Whereas **eclipsed conformation** has the maximum potential energy.

STEREOCHEMISTRY

- The term ***anti elimination*** means that the proton and leaving group depart from opposite sides of the bond, which then becomes a double bond.
- The term ***syn elimination*** means that the depart from the same side.



syn elimination
(dihedral angle 0°)

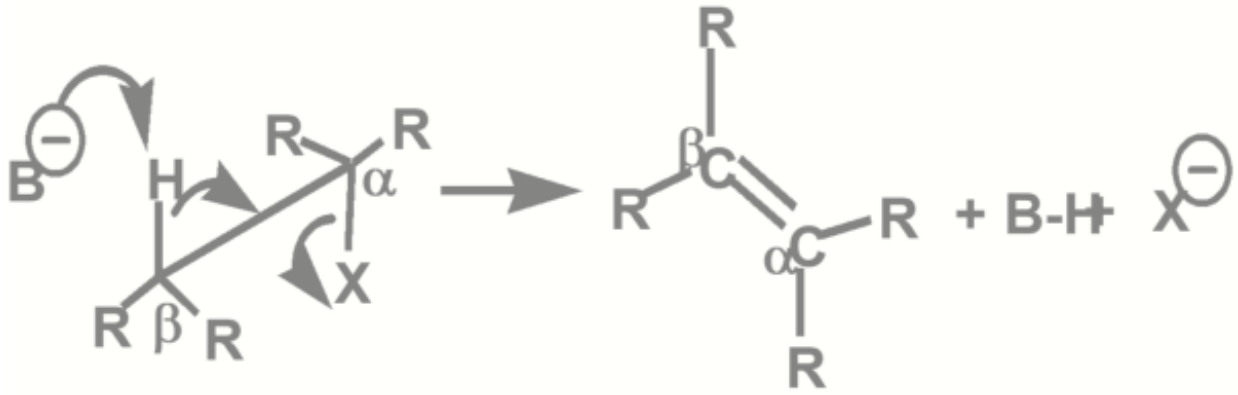
anti elimination
(dihedral angle 180°)

- **E2 reactions** are highly stereospecific and *anti elimination* is preferred over syn elimination
  - In anti E substrate has staggered conformation while that of in syn is eclipsed.

STEREOCHEMISTRY

Anti Elimination in E2

- ***Antiperiplanar;*** *the H and X groups must be anti to each other and be in the same plane with each other and the carbon atoms* to which they are attached.

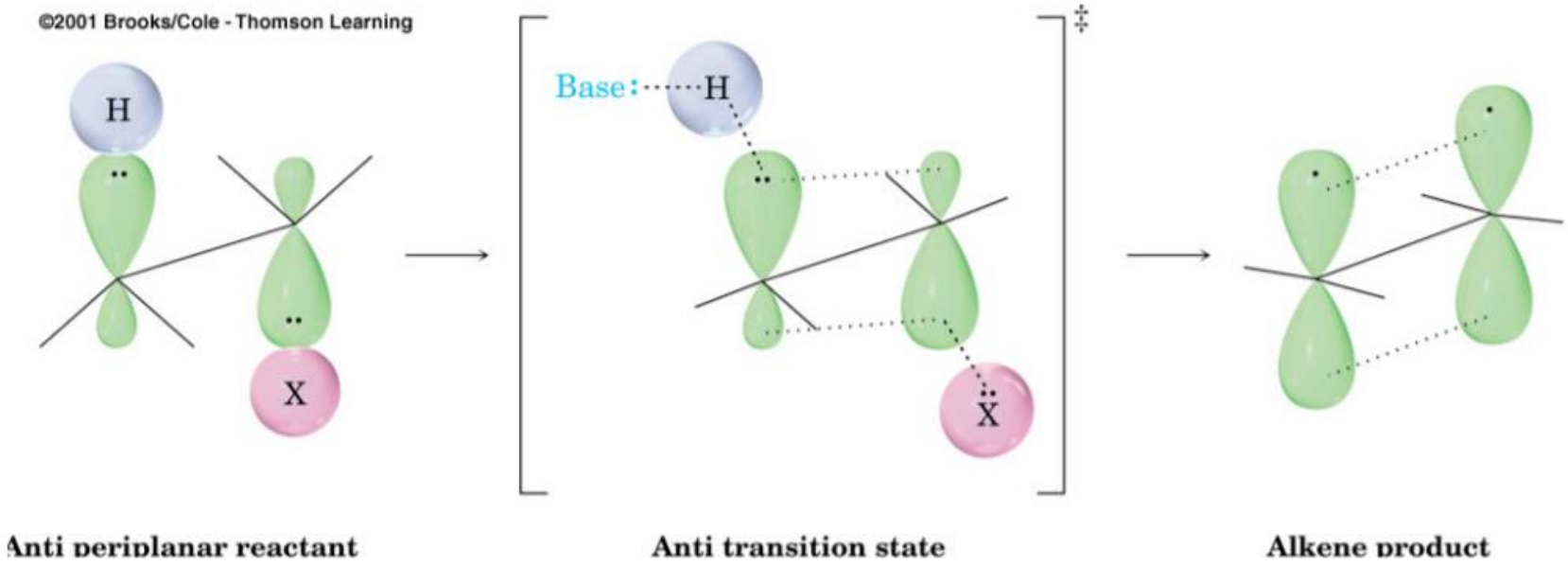


- The **anti-position** *allows the transition state of the reaction is in the more stable staggered conformation (helps to lower down the energy level of the transition state and speed up the reaction).*

STEREOCHEMISTRY

Anti Elimination in E2

- Antiperiplanar allows orbital overlap and minimizes steric interactions

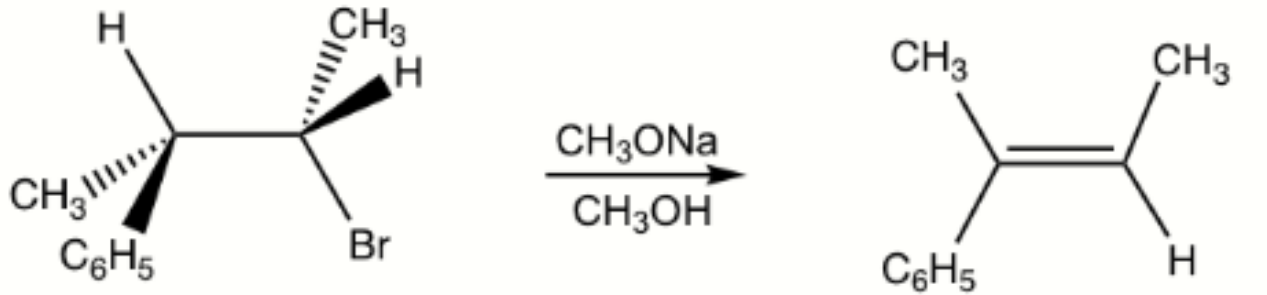


- In the periplanar conformation, the orbitals are already aligned for π-bond formation

STEREOCHEMISTRY

Anti Elimination in E2

- **E2 reactions** are stereoselective, resulting in the formation of *trans-double bonds* preferably.
- **Example;** the elimination of (2S,3S)-2-bromo-3-phenylbutane produces the ***E*** isomer specifically, not the ***Z*** isomer at all.



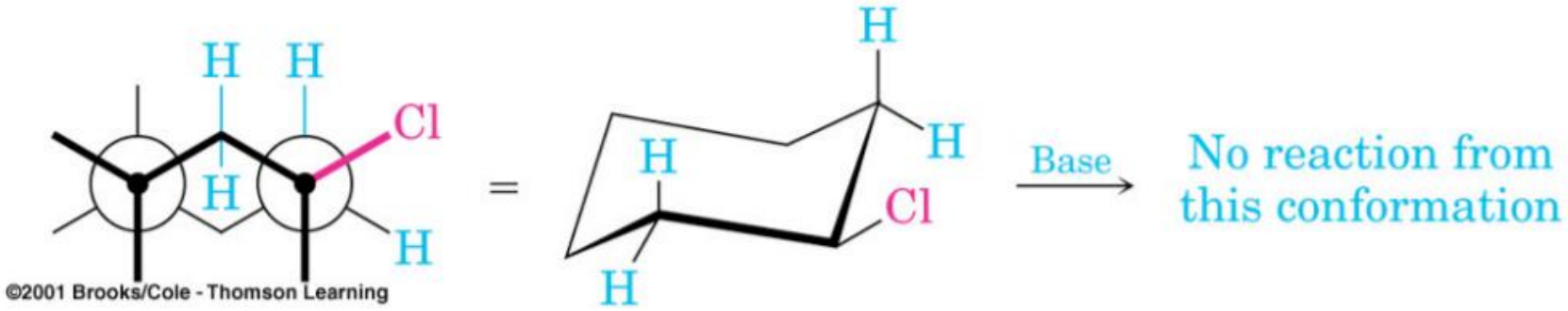
(2*S*,3*S*)-2-bromo-3-phenylbutane **(*E*)-2-phenyl-2-butene**

*This is because when H is in anti-position to the leaving group Br, the whole compound is in staggered conformation, and the other groups retain their relative position in elimination that leads to the **E** isomer.*

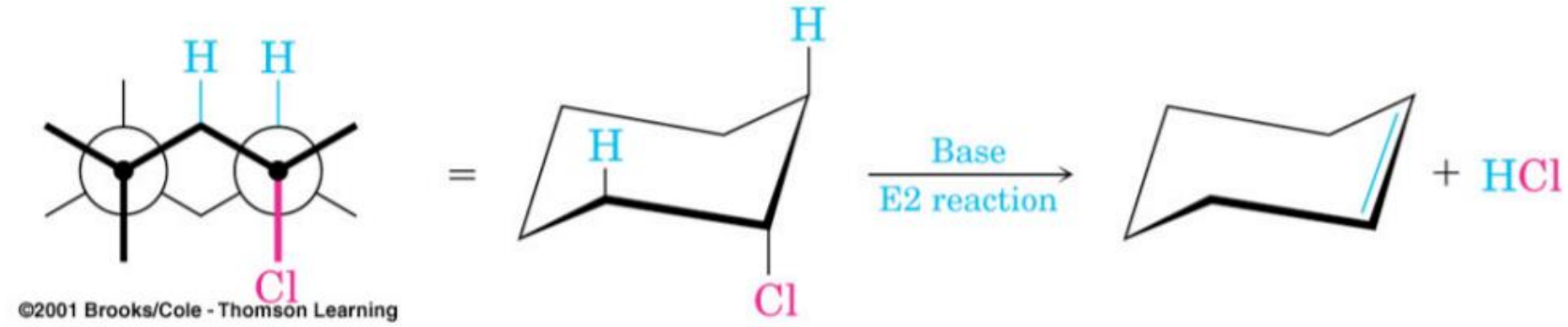
STEREOCHEMISTRY

E2 Elimination with Halocyclohexane Reactants

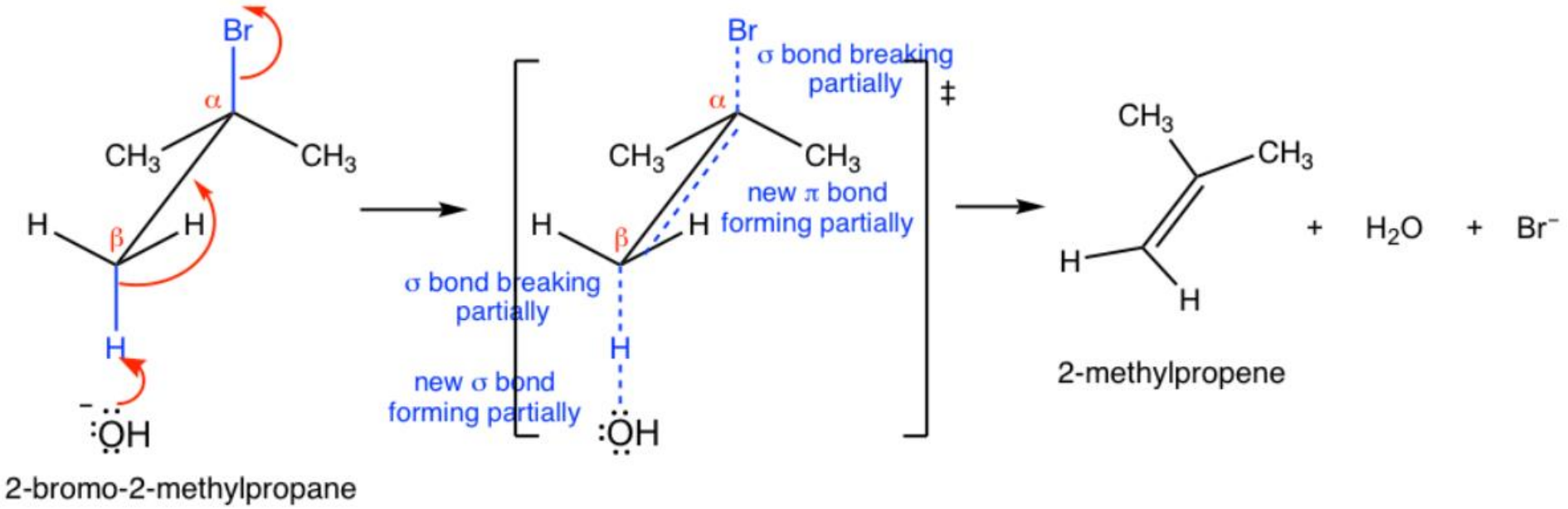
Equatorial chlorine: H and Cl are not anti periplanar



Axial chlorine: H and Cl are anti periplanar



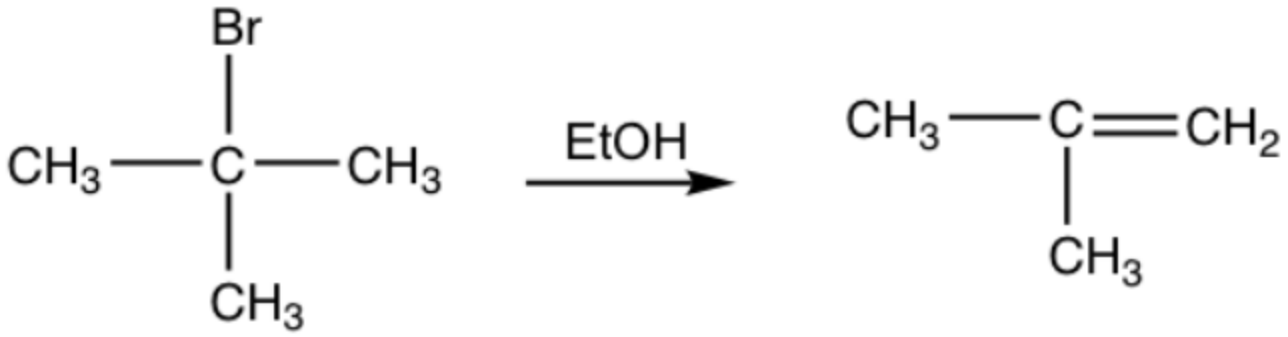
SUMMARY



- **Reaction is:**
  - Stereospecific (Anti-periplanar geometry preferred, Syn-periplanar geometry possible)
  - Concerted - all bonds form and break at the same time
  - Bimolecular - rate depends on concentration of both base and substrate
  - Favored by strong bases

REACTION

- When *t*-butyl bromide reacts with ethanol, small amount of elimination products obtained via E1 mechanism.



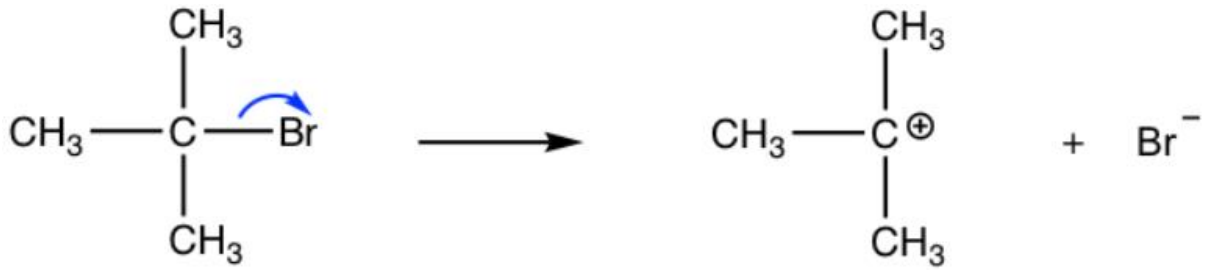
Reaction Rate = *k* x $[(CH_3)_3Br]$ **first-order reaction**

REACTION MECHANISM

- The overall elimination involves two steps:

Step 1: Cleavage of C-Br bond **slowly** to form the carbocation intermediate.

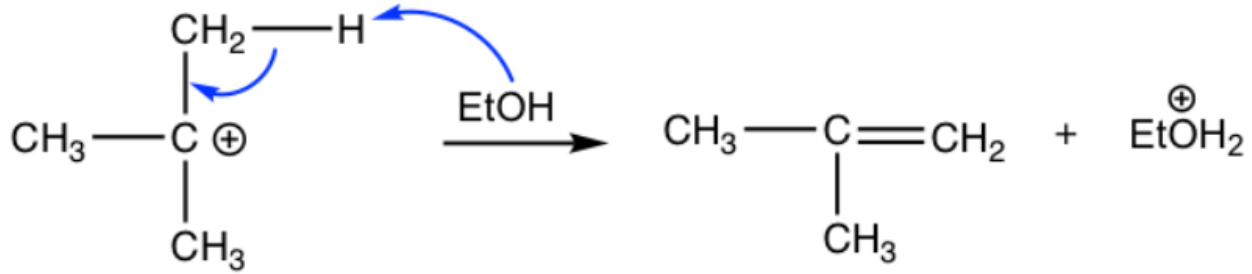
Spontaneous dissociation of the tertiary alkyl bromide yields carbocation intermediate in a slow, rate-determining step



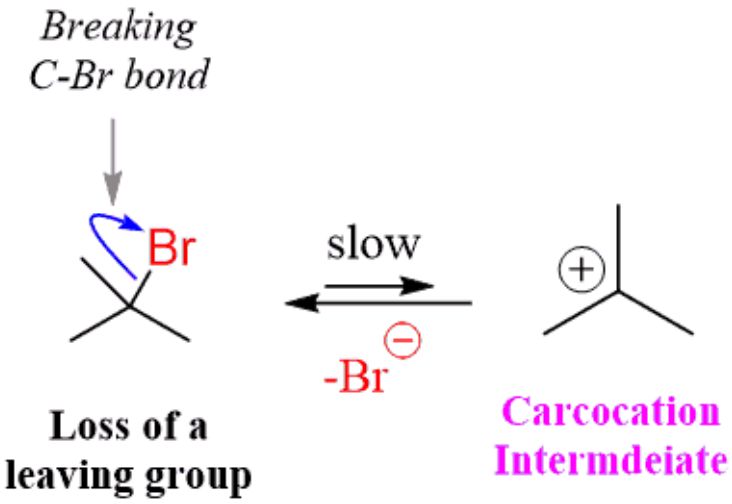
carbocation intermediate

Step 2: base (Et-OH) removes H from β–carbon, and double bond produced.

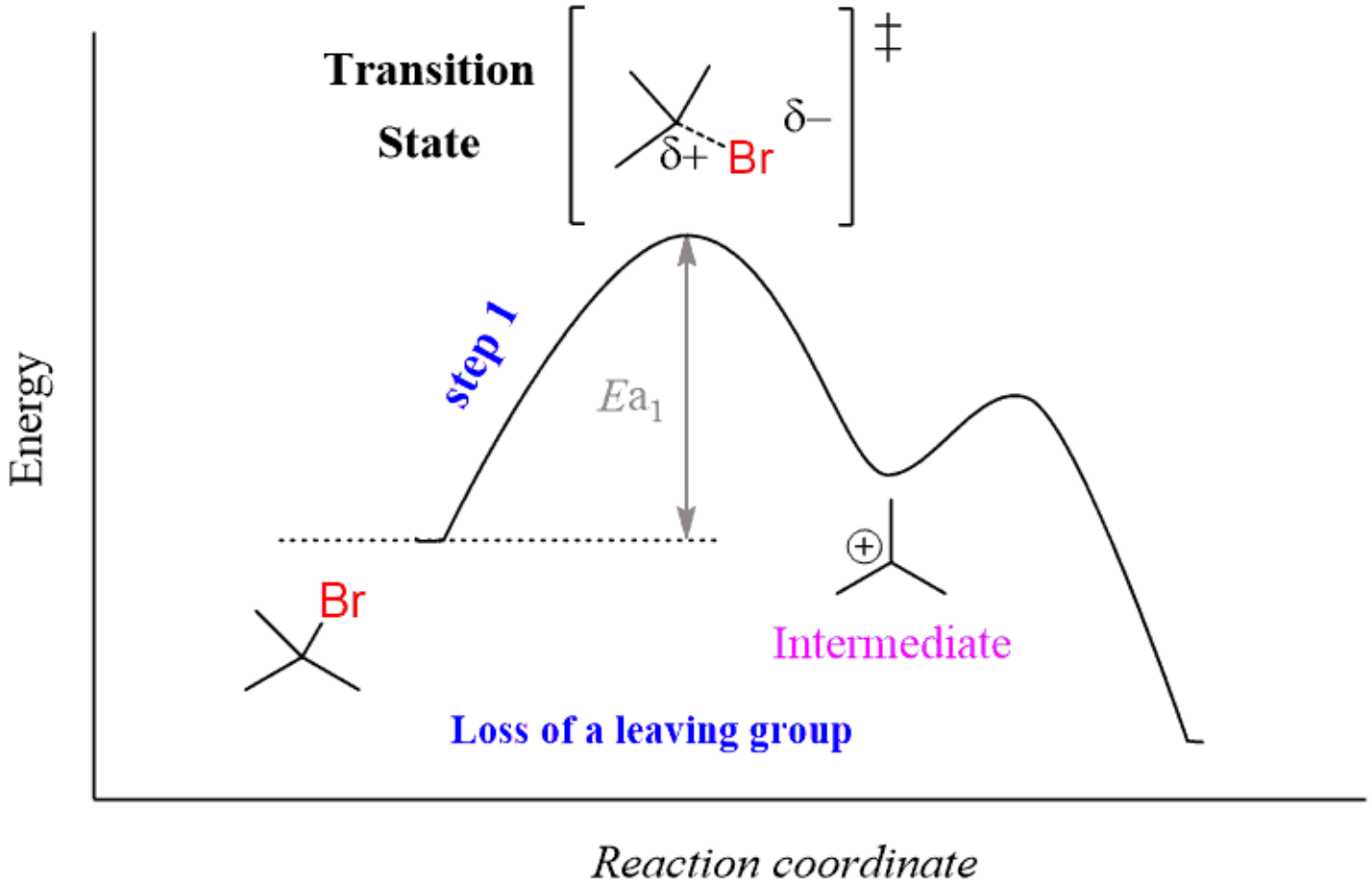
Loss of a neighboring H+ in a fast step yields the neutral alkene product.
The electron pair from the C-H bond goes to form the alkene π–bond.



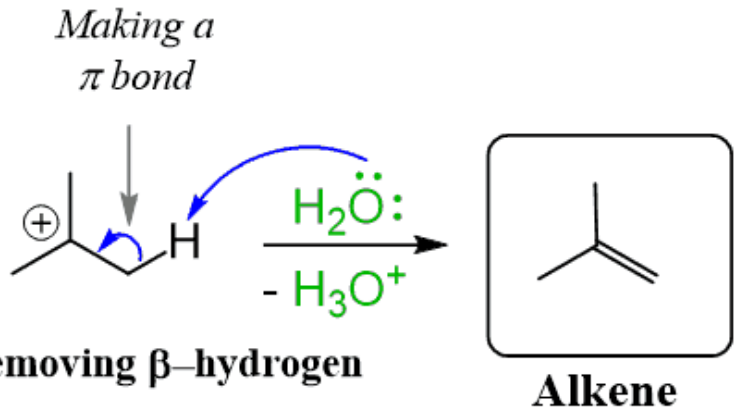
ENERGY PROFILE DIAGRAM



The energy diagram showing the first step of the E1 mechanism

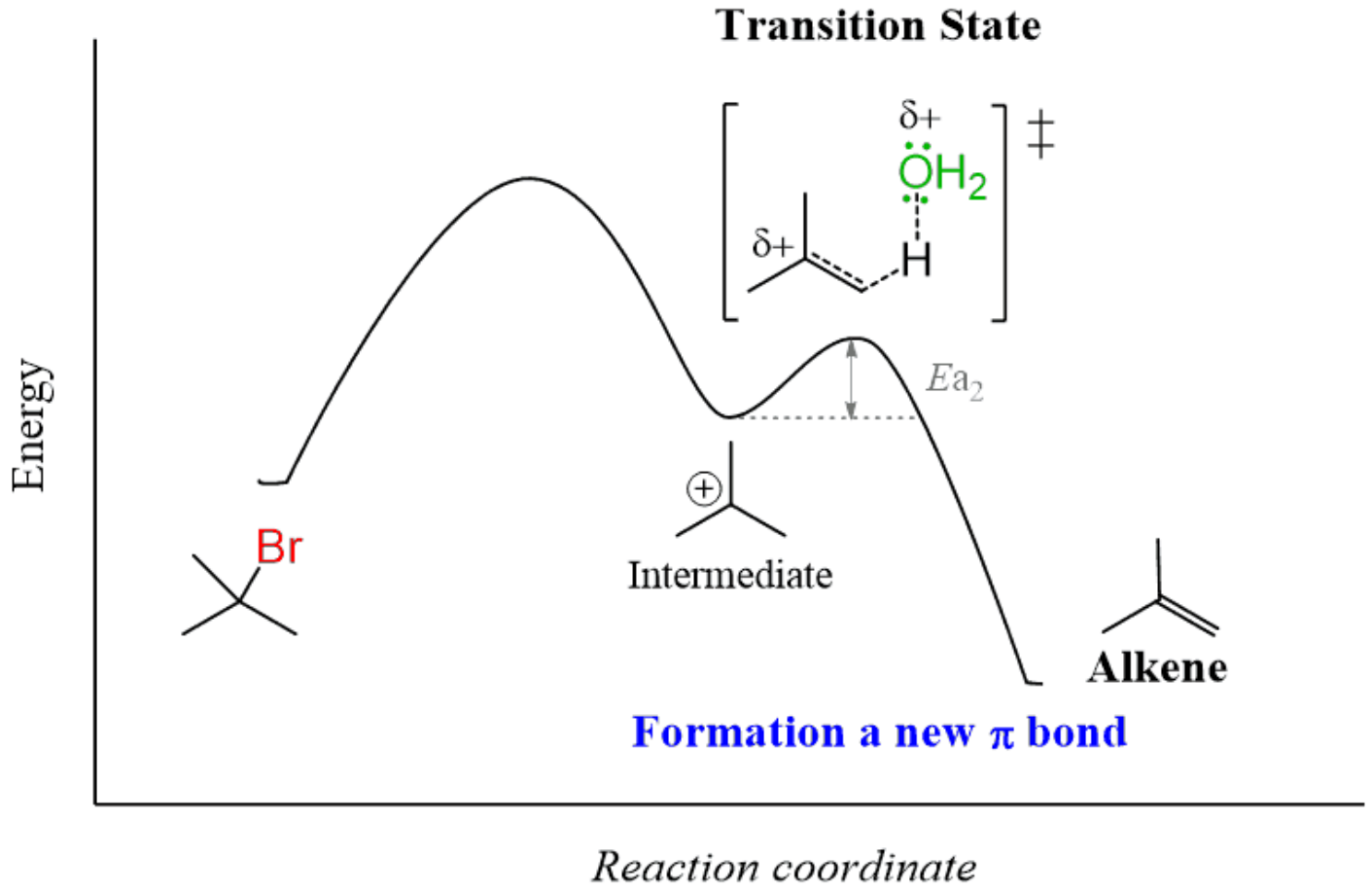


ENERGY PROFILE DIAGRAM



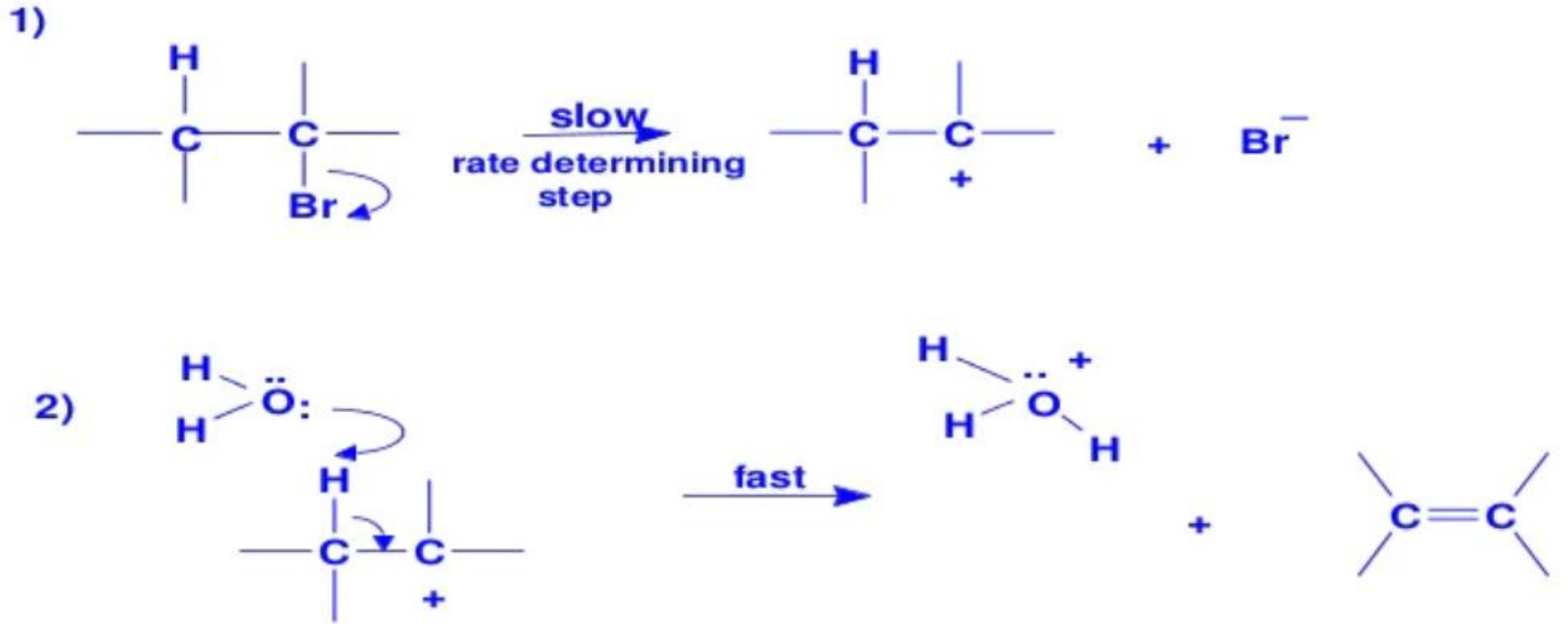
E1, the carbocation undergoes and acid-base reaction.

The energy diagram showing the formation of the π bond



REACTION KINETICS

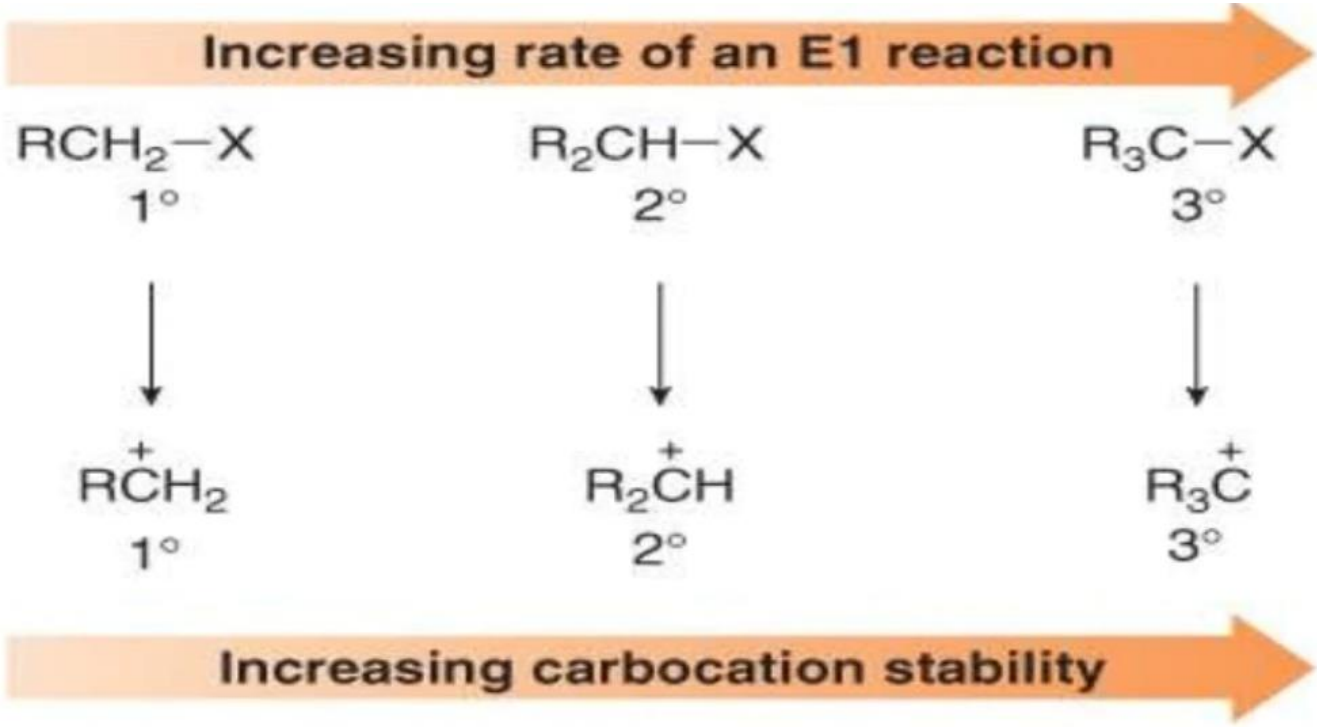
- E1 reactions follow first order (unimolecular) kinetics.
- Rate = k [R-X]
- The solvent helps to stabilize the carbocation, but it does not appear in the rate law



FACTORS AFFECTING THE RATE OF E1 REACTION

1) Substrate Effect

- The order of the reactivity of the alkyl groups is: Tertiary > Secondary > Primary
- This is because the rate-determining step is the formation of carbocation and the stability of these ions increases; Tertiary > Secondary > Primary
- It is hard (but not impossible) to get primary carbocations are not stable.

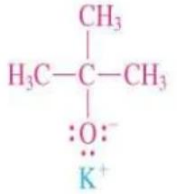


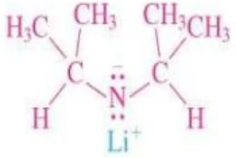
FACTORS AFFECTING THE RATE OF E1 REACTION

2) Base Effect

- Bulky bases favor elimination

Sterically Hindered Bases

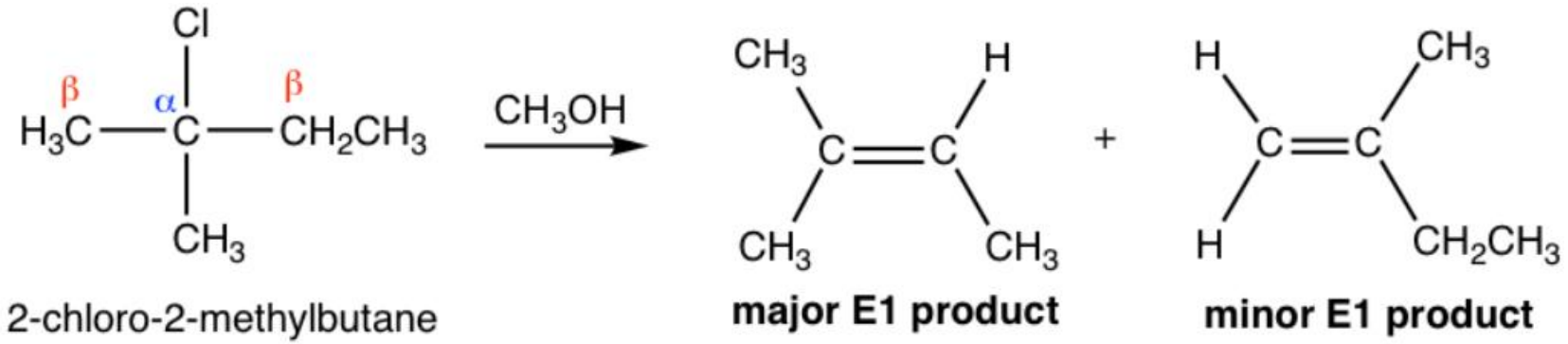




FACTORS AFFECTING THE RATE OF E1 REACTION

3) Orientation of Elimination: Zaitsev's Rule

- E1 reactions follow Zaitsev's rule
- The major product should be the product that is the most highly substituted.



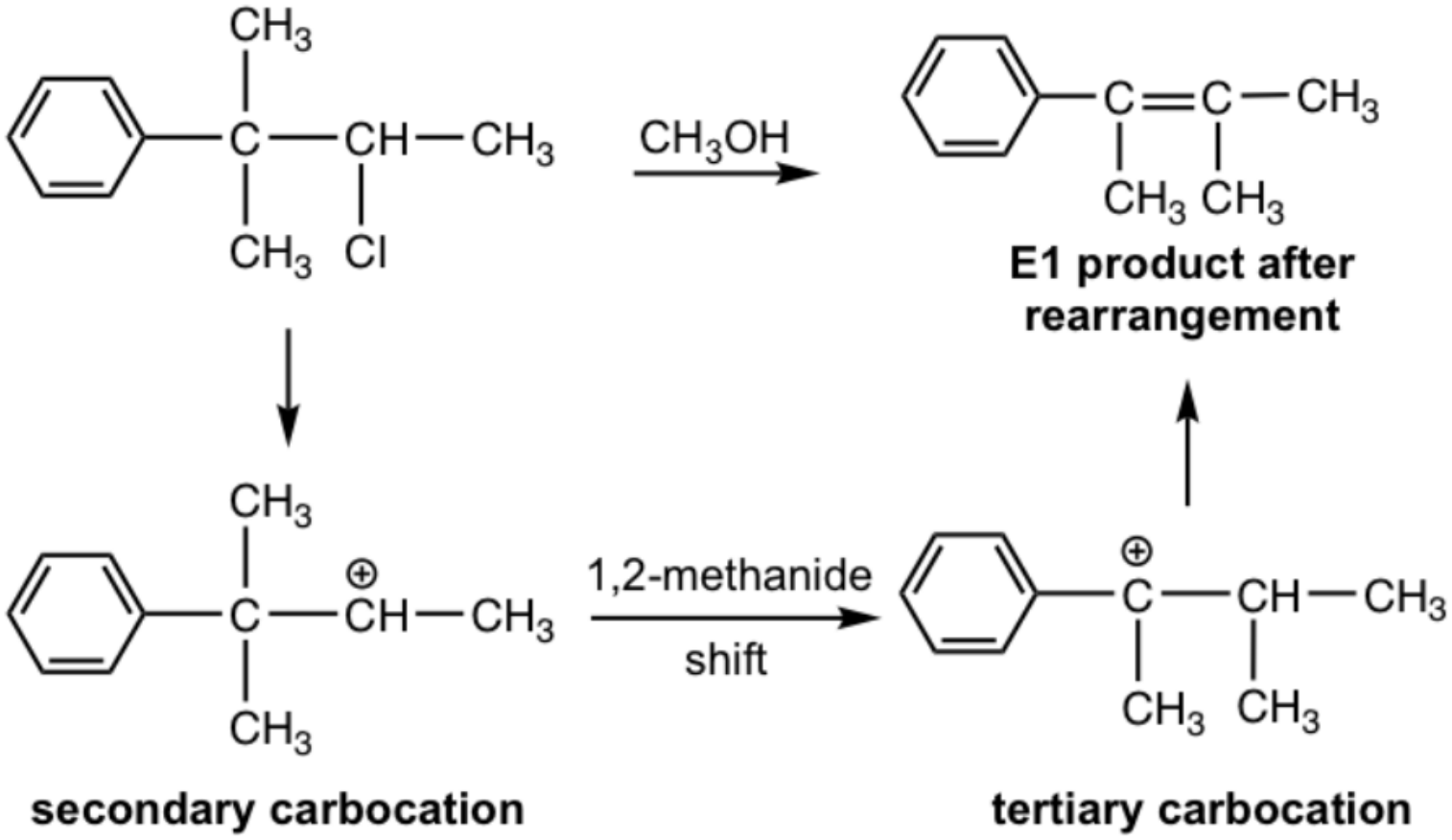
2-chloro-2-methylbutane

major E1 product

minor E1 product

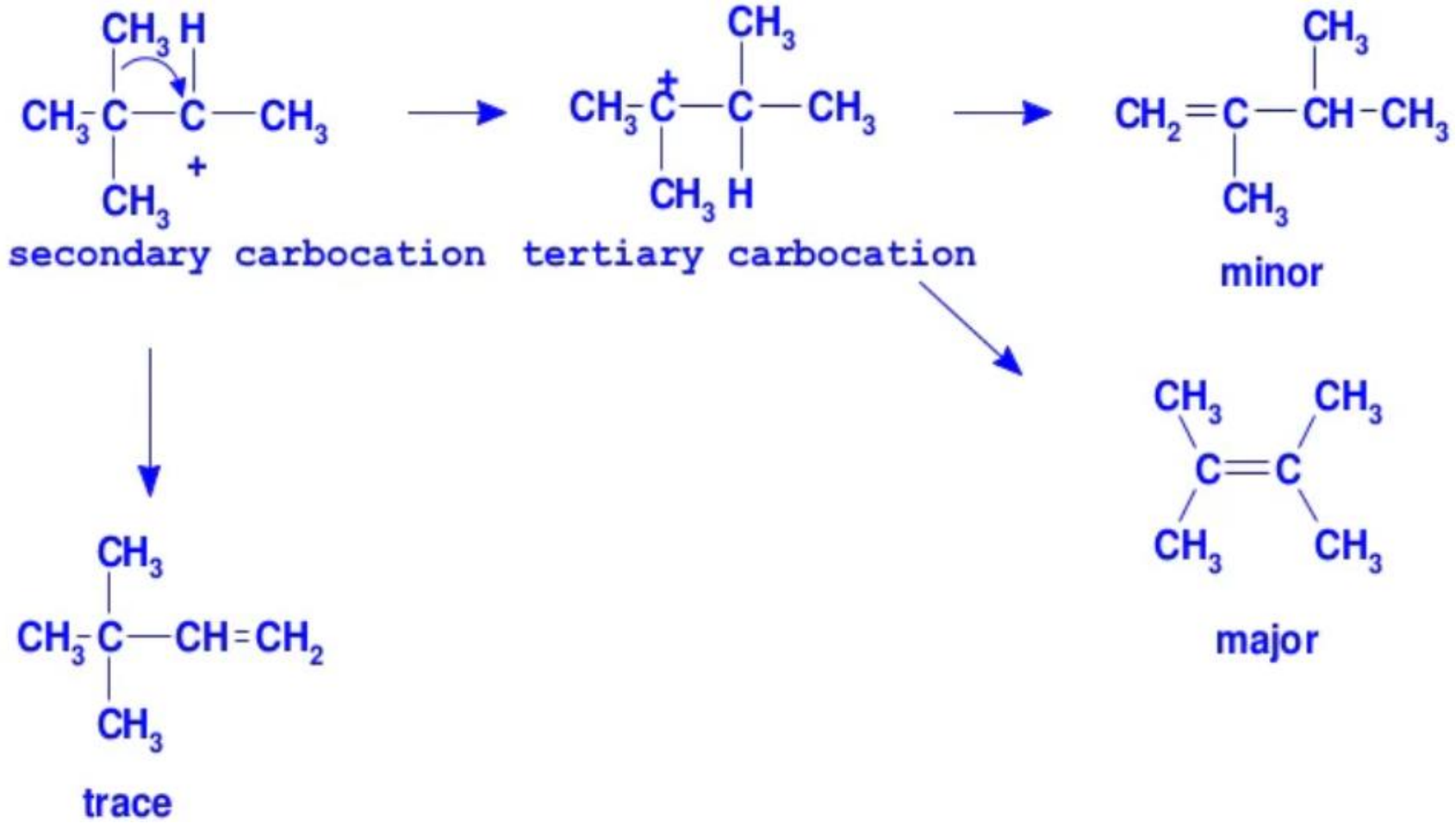
REARRANGEMENTS

- Since E1 reaction involves a carbocation intermediate, the carbocation rearrangement might occur if such rearrangement leads to a more stable carbocation.

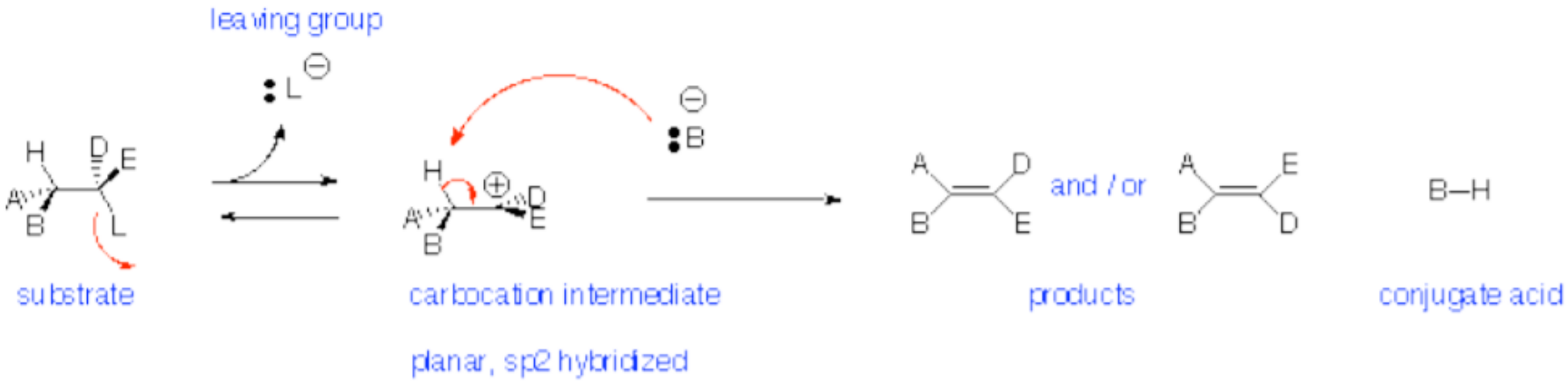


REARRANGEMENTS

- Alkyl groups and hydrogen can migrate in rearrangement reactions to give the more stable intermediate carbocations.



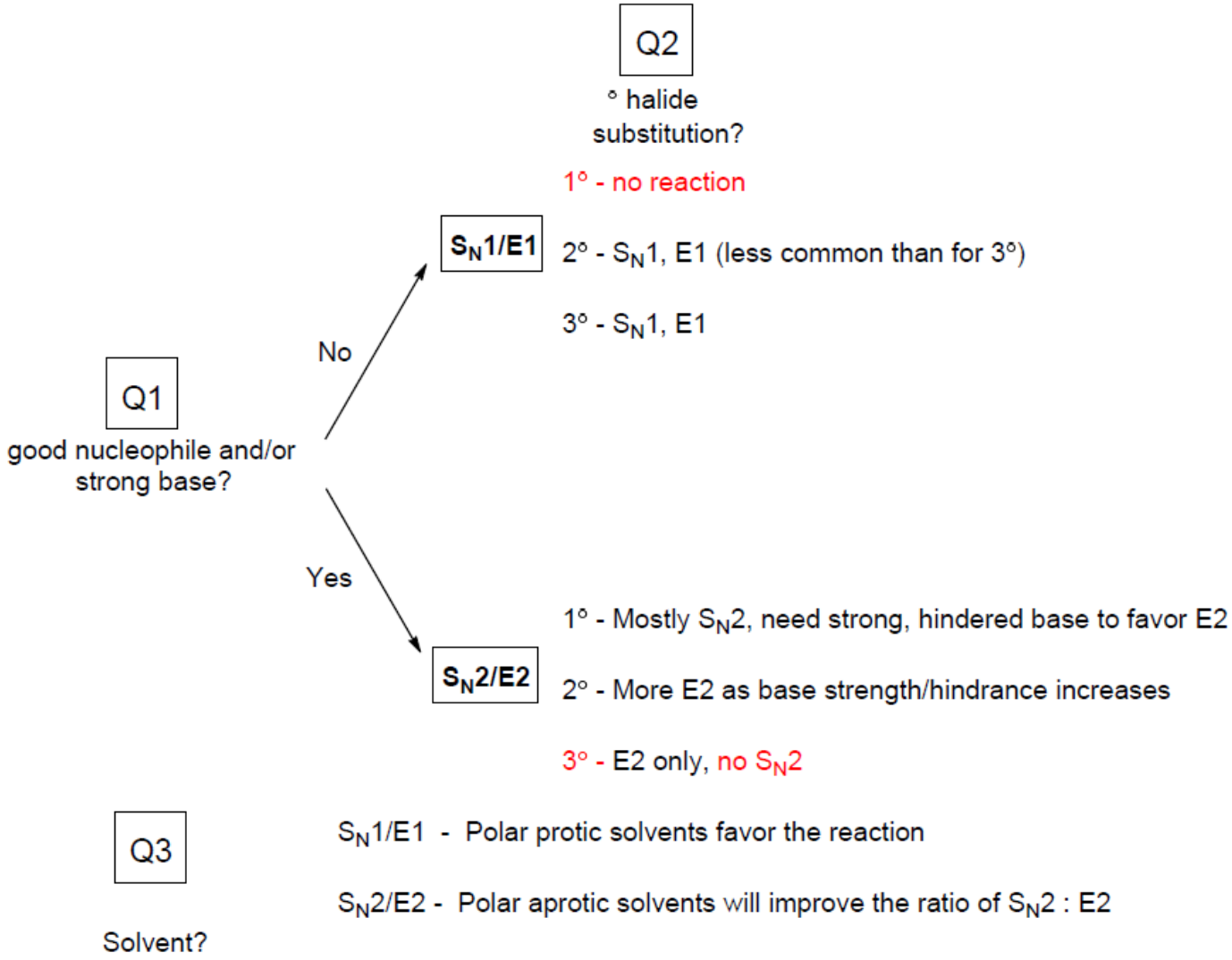
SUMMARY



- **Reaction is:**
  - Non-stereospecific- follows Zaitsev (Saytseff) Rule
  - Non-concerted - has carbocation intermediate - favoured for tertiary leaving
  - groups
  - Unimolecular - rate depends on concentration of only the substrate
  - Does NOT occur with primary alkyl halides (leaving groups)
  - Strong acid can promote loss of OH as H2O or OR as HOR if tertiary or
  - conjugated carbocation can be formed

SUBSTITUTION / ELIMINATION FLOWCHART

- Ask these three questions:



SUBSTITUTION or ELIMINATION

SUMMARY OF ALKYL HALIDES AND S_N1, S_N2, E1 AND E2 MECHANISMS

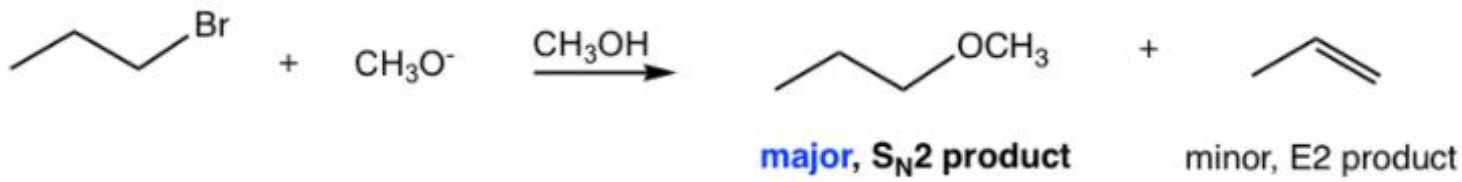
Alkyl halide type	Reaction with		Mechanism
1° RCH_2X	• Strong nucleophile	--→	S_N2
	• Strong bulky base	--→	E2
2° R_2CHX	• Strong base and nucleophile	--→	S_N2 and E2
	• Strong bulky base	--→	E2
	• Weak base and nucleophile;	--→	S_N1 and E1
3° R_3CX	• Weak base and nucleophile	--→	S_N1 and E1
	• Strong base	--→	E2

COMPARISON and COMPETITION BETWEEN S_N1, S_N2, E1 & E2

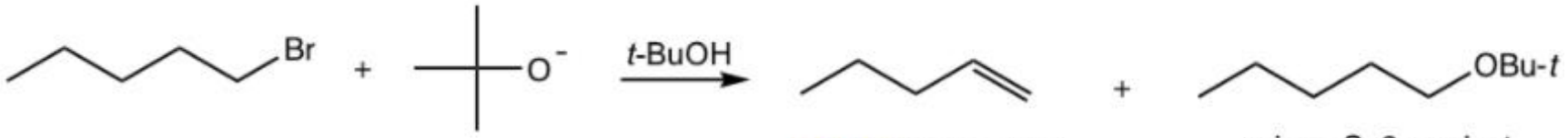
STRUCTURAL NATURE OF A SUBSTRATE (PRIMARY, SECONDARY OR TERTIARY)

- **Methyl substrate** only go with S_N2 reaction,
- **Primary (1°) substrates**
  - cannot go with any unimolecular reaction, (e.g. no S_N1/E1),

    because primary carbocations are too unstable to be formed.
  - **S_N2 is the predominant pathway when good nucleophile is used**; Cl^-, Br^-, I^-, RS^-, N_3^-, CN^-, RCO_2^-.
  - **E2** becomes the major reaction when **big bulky base/nucleophile** is used; *t*-BuO^- and LDA



major, S_N2 product minor, E2 product



major, E2 product minor, S_N2 product

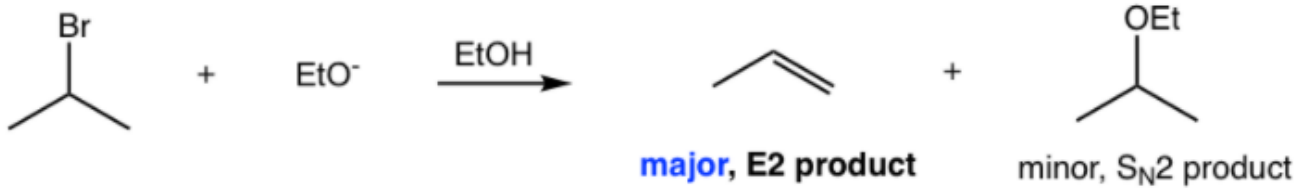
COMPARISON and COMPETITION BETWEEN S_N1, S_N2, E1 & E2

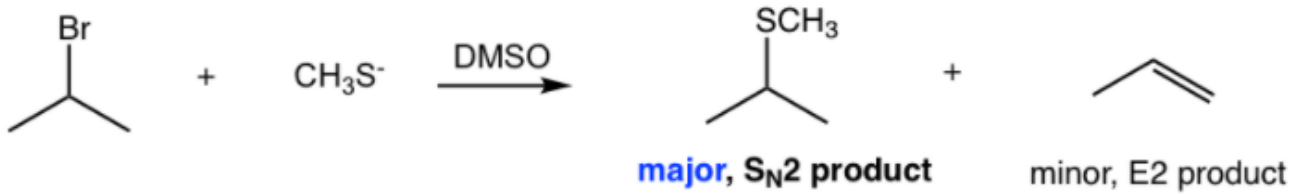
STRUCTURAL NATURE OF A SUBSTRATE (PRIMARY, SECONDARY OR TERTIARY)

- **Secondary (2°) substrates**
  - It is most complicated or challenging because all the pathways are possible.
  - **E2:** favored by a strong base; ^-OH, RO^-(R: small size alkyl group), NH_2^-
  - **S_N2:** favored by a **good nucleophile (relatively weaker base);** Cl^-, Br^-, I^-, RS^-, N_3^-, CN^-, RCO_2^-.
  - **S_N1/E1**: It is hard to separate S_N1 and E1 completely apart, because they both go through **carbocation intermediates**, and are favored by **poor nucleophile/weak base**; H_2O or ROH (solvolysis).

    S_N1 and E1 usually occur together for secondary substrates, and

    increasing the reaction temperature favors E1 over S_N1.



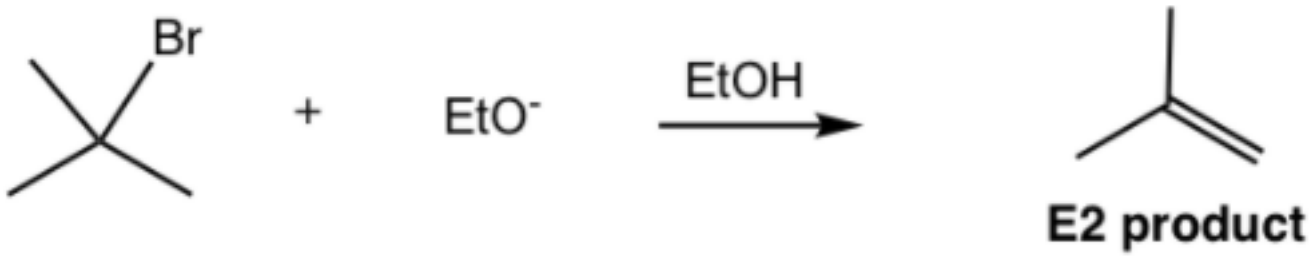


COMPARISON and COMPETITION BETWEEN S_N1, S_N2, E1 & E2

STRUCTURAL NATURE OF A SUBSTRATE (PRIMARY, SECONDARY OR TERTIARY)

- Tertiary (3°) substrates
  - do not go with S_N2 reactions because of **steric hindrance**.
  - **E2** reaction is the choice when **strong base** applied; ; ^-OH, RO^-(R: small size alkyl group), NH_2^-
  - **S_N1/E1** pathway with neutral condition (poor nucleophile/weak base); H_2O or ROH (solvolysis).

    E1 always combine together with S_N1, and it is almost impossible to avoid the substitution product.



NOTES:

- The relative stronger bases have the stronger tendency to act as base.
- The relative weaker base, with small size and good polarizability, have the better tendency to act as nucleophile.
- Bulky bases, such as *t*-BuO^- and LDA, always favor E2 and generate elimination products that follow Hofmann rule, because they are too big to do back-side attack in S_N2.